

# Lawrence Berkeley National Laboratory

## LBL Dissertations

**Title**

THE EFFECT OF HIGHLY IONIZING RADIATIONS ON CELL SURVIVAL

**Permalink**

<https://escholarship.org/uc/item/2rw4482k>

**Author**

Sayeg, Joseph A.

**Publication Date**

1954-04-01

Thesis/dissertation

UNIVERSITY OF  
CALIFORNIA

*Radiation  
Laboratory*

TWO-WEEK LOAN COPY

*This is a Library Circulating Copy  
which may be borrowed for two weeks.  
For a personal retention copy, call  
Tech. Info. Division, Ext. 5545*

BERKELEY, CALIFORNIA

## **DISCLAIMER**

This document was prepared as an account of work sponsored by the United States Government. While this document is believed to contain correct information, neither the United States Government nor any agency thereof, nor the Regents of the University of California, nor any of their employees, makes any warranty, express or implied, or assumes any legal responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by its trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof, or the Regents of the University of California. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof or the Regents of the University of California.

UNIVERSITY OF CALIFORNIA

Radiation Laboratory  
Berkeley, California

Contract No. W-7405-eng-48

THE EFFECTS OF ACCELERATED CARBON NUCLEI AND OTHER  
RADIATIONS ON THE SURVIVAL OF HAPLOID YEAST

PART I. DOSIMETRY OF THE CYCLOTRON BEAMS

Ann C. Birge and Joseph A. Sayeg

PART II. BIOLOGICAL EXPERIMENTS

Joseph A. Sayeg, Ann C. Birge, Carl A. Beam,  
and Cornelius A. Tobias

July 1958

THE EFFECTS OF ACCELERATED CARBON NUCLEI AND OTHER RADIATIONS ON THE  
SURVIVAL OF HAPLOID YEAST. I. DOSIMETRY OF THE CYCLOTRON BEAMS.<sup>1</sup>

by

Ann C. Birge and Joseph A. Sayeg<sup>2</sup>

Donner Laboratory of Biophysics and Medical Physics

University of California, Berkeley

copies:

pages:

figures: 9

tables: 1

Proposed running head: EFFECTS OF HEAVY PARTICLES ON YEAST

Proofs to be sent to: Dr. Ann C. Birge  
Donner Laboratory  
University of California  
Berkeley 4, California

## INTRODUCTION

It is well known that the effects of ionizing radiation on a biological system are not only dependent on the energy delivered to the system, i.e., the total dose, but also on the spatial distribution of that energy. There have been many studies of relative biological effectiveness (RBE) between radiations of different rates of energy loss or linear energy transfer (LET) (1, 2), but there are only a few instances in which the same biological system has been studied systematically with a wide range of radiations. In the investigation reported here cell survival of the haploid yeast, Saccharomyces cerevisiae, was studied for LET values ranging between 2 and 500 kev per micron. It is not possible to obtain such high and uniform values of LET with conventional radiations such as polonium alpha particles. Furthermore, the dose is uncertain near the Bragg ionization peak, where the LET varies rapidly with absorber thickness. Hence for this study we used the beams available at the Berkeley 60-inch cyclotron: 20-Mev deuterons, 40-Mev alpha particles, and 120-Mev carbon nuclei with mass 12 and charge 6 (3), in addition to x-rays and polonium alpha particles.

For any study of relative biological effectiveness it is essential to have accurate dose measurements for all the radiations used. The successful measurement of dose from a cyclotron beam depends on a series of physical measurements to determine the beam characteristics. For this purpose equipment was designed to measure Bragg ionization curves and particle ranges as a function of absorber thickness, and a special ionization chamber was built to measure the dose to biological samples. Special emphasis was placed on the work with the carbon particles because of their uniqueness and the difficulties inherent in their use. The first paper of this pair deals with the physical problem of determining the linear energy transfer and the doses delivered by the various cyclotron beams.

The second paper describes the biological experiments and their results, including additional data obtained with 50-kv and 220-kv x-rays, as well as  $\text{Po}^{210}$  alpha particles.

Because the frequency of the 60-inch cyclotron is fixed, the resonance conditions for accelerating particles of slightly different charge-to-mass ratio are satisfied by adjusting the magnetic field. For ions that originate with their full charge at the ion source -- e.g. deuterons and alpha particles -- the resonance peak is sharp and the machine can be adjusted to give a known beam with only a small spread in energy. For carbon ions, however, the voltages in the ion source are not sufficient to strip off all the electrons. Since the cyclotron resonance conditions are met by carbon ions with a charge of 2 as well as by those with a charge of 6, it is believed that the ions to be accelerated leave the ion source with a charge of 2 and are converted to a charge of 6 after gaining some energy (4). As a consequence, the magnetic-field resonance for carbon ions is not a sharp peak in the position expected from calculations of the charge-to-mass ratio, but is a very broad maximum that overlaps the sharp resonance peak of the alpha particles. Hence the mean energy and energy spread of carbon particles in the external beam are determined by the position and width of slits in the external equipment, which in our experiments was located in the fringing magnetic field of the cyclotron. During each run measurements were made to determine the beam energy and hence the LET, and to be sure that the number of alpha particles mixed with the carbon ions was negligible. Measurements were also made to determine the intensity distribution of the beams to ensure adequate uniformity over the area of the biological samples. Various other checks were made to provide accurate dose measurements for each run.

# EXPERIMENTAL ARRANGEMENT

Figure 1 shows a schematic plan view of the cyclotron with our equipment for using the external beams. The ions originally formed at the ion source,  $I_s$ , are accelerated by the oscillating electric field between the dees, and are held in spiral trajectories by the magnetic field of the cyclotron. Those particles which come down the deflector channel with suitable energy pass through the series of adjustable slits,  $S_1$ ,  $S_2$ , and  $S_3$ , which are needed to exclude particles of unsuitable energy or charge-to-mass ratio. The beam passes out of the vacuum system through the thin dural window  $W$  into the monitor ionization chamber  $I_1$ , thence through the aluminum absorbers controlled remotely in the pair of selector wheels, and finally through the analyzer ionization chamber  $I_2$ . The sample to be irradiated is placed behind the second ionization chamber. The position of the evacuated snout and the attached ionization chambers can be adjusted remotely in a horizontal plane by bending the two sylphon bellows,  $B_1$  and  $B_2$ , and in a vertical plane by raising or lowering the supporting 1/4-inch dural plate with adjustment screws. Thus the equipment can be moved to center the beam in the ionization chambers. In Fig. 2 is shown a photograph of this equipment in place between the magnet coils of the cyclotron.

For measuring the range and specific ionization of the carbon particles, ionization chambers were constructed in which individual particle pulses could be counted. The beam passed through the ionization chambers in a direction parallel to the collection of charge, so that a uniform pulse height was produced by particles passing through different parts of the chamber. The monitor ionization chamber,  $I_1$ , consisted of two 0.00025-inch-thick aluminum foils, spaced 29/32 inches apart, with an effective area 1-1/4 inches in diameter. Teflon insulation and a grounded guard ring between the high-voltage foil and collector foil minimized leakage currents. The chamber was housed in a brass cylinder

which also supported the coaxial connectors to the high-voltage supply and to the electronic equipment.

For much of the work the analyzer ionization chamber was identical to the monitor chamber. The best results were obtained, however, with a pair of analyzer chambers. The first analyzer chamber, only 1/8-inch thick, was used for integrating the total charge produced. Such a thin chamber gives good resolution for measuring the average specific ionization produced by the particles. An adjacent thick chamber with 0.82-inch spacing was used for counting individual particle pulses. The large collection space was necessary in order that an individual particle would produce enough ions to be counted as a pulse above the noise level of the electronic equipment. The two chambers were separated by a thin aluminum foil, weighing  $1.6 \text{ mg/cm}^2$ . In these chambers the collector foil was placed between a pair of high-voltage foils, and was constructed of aluminum leaf,  $0.12 \text{ mg/cm}^2$  in thickness. The voltage on the foils was adjusted so that the electric field was the same in all parts of the chambers.

The charge collected in each ionization chamber was determined by measuring the voltage produced across a known capacitance or resistance with an integrating electrometer. Since the electrometer held the collector plate effectively at ground potential, a constant voltage was supplied to the ionization chamber. At the same time the total charge or ionization current was being measured, the individual pulses were fed through a low-capacity cable and blocking condenser to a preamplifier located just outside the magnetic field of the cyclotron, and into a linear amplifier and scaler. A Tektronix oscilloscope was used to monitor the output pulses visually.

To minimize problems of ion recombination and assure fast electron collection, the formation of negative ions was prevented by flowing dry nitrogen

gas through the ionization chambers at a slow rate. Curves of ionization current as a function of collection voltage showed that with a voltage gradient of 1000 volts per cm the chambers were being operated in the region of saturation, where a negligible number of ions was being lost by recombination. Typical voltage saturation curves <sup>are</sup> shown in Fig. 3. Observation of the heights and shapes of individual particle pulses as functions of collection voltage showed that the charge was collected in a time shorter than the amplifier rise time, and supported the conclusion that fast electron collection was maintained at the voltages used.

The counting rate for a given amplifier gain is a function of the discriminator-bias setting on the scaler. For both ionization chambers a curve of counting rate as a function of bias setting showed a broad plateau, approximately 20 volts wide, where amplifier noise pulses were excluded but carbon-particle pulses were counted. Although special precautions were taken to minimize amplifier noise, calculations showed that a particle had to lose nearly 1 Mev in the ionization-chamber gas in order to produce a pulse barely visible at the lower end of the plateau curve. The final bias settings used were far enough up on the plateau so that a small shift in bias voltage would produce a negligible change in counting rate; the settings for different runs corresponded to energy losses between 1.5 and 2.5 Mev.

Because of the fringing magnetic field of the cyclotron, the various beams were confined to a vertical dimension between  $1/8$  and  $1/4$  inch, but extended horizontally across the full  $3/4$  inch allowed by the defining aperture  $S_3$  in Fig. 1. Since it is important to have the radiation as nearly as possible uniform in intensity over the biological sample, a profile-scanning apparatus was used to measure the intensity distribution of the cyclotron beams. This apparatus consisted of a movable aluminum flag,  $1/16$ -inch thick, with a  $1/32$ -inch ~~aperture~~

circular aperture at the center, and was inserted between the absorber wheels and the second ionization chamber. The flag could be moved by remote control from outside the cyclotron target area. For each experiment a series of beam profiles was taken, each consisting of a plot of relative beam intensity as the scanning aperture was moved horizontally or vertically across the radiation field. Figures 4 and 5 show profiles of the carbon and alpha-particle beams obtained in this manner. The peculiar pattern shown in Fig. 5 was apparently related to the operating conditions of the cyclotron, and was most persistent for the alpha particles. For carbon particles, which exhibited a very broad cyclotron resonance, such a nonuniform pattern was avoided by adjustment of the position of the external equipment.

Because of the peculiar distribution of the beam, its alignment with respect to the biological samples was critical; therefore a special quadrant ionization chamber was constructed for measuring the dose and indicating the beam alignment during the actual biological irradiations. The design of this plane parallel chamber, 17/32 inch deep, was basically similar to the monitor ionization chamber, except that the collector foil was divided into a central region -- smaller than the dimensions of the beam -- and four surrounding quadrant plates, shown schematically in Fig. 6. The area of the central 0.0005-inch aluminum collector foil, very nearly a rectangle 13.4 mm wide by 3.8 mm high, was measured accurately with a traveling microscope, and served to define the collection volume used in the dose calculation. The biological sample consisted of cells plated on the surface of an agar block 9.9 mm by 2.6 mm, and was smaller in area than the collector foil. The sample was accurately positioned just behind the foil (see Fig. 7). The four quadrant electrodes were made of a conducting layer of silver paint on teflon backing. When the ionization current collected from the top quadrant equaled that

from the bottom, and the current from the left equaled that from the right, the beam was assumed to be centered over the collector and hence over the biological sample. Since the beam had to be turned off while the samples were changed, it was important to check the beam alignment during each bombardment. As with the other chambers, a continuous flow of dry nitrogen gas was maintained. For each experiment a curve of ion current as a function of collection voltage (Fig. 3) showed that the chamber was being operated in the region of saturation for the collection voltage of 2000 volts.

#### PHYSICAL MEASUREMENTS

In order to do practical biological experiments with the external beam of carbon particles, it was necessary to use the maximum beam obtainable, which gave dose rates around 1000 rads per min. To obtain the maximum beam, and because of variations in cyclotron operating conditions between different runs, many measurements and adjustments had to be made during each run before the beams could be used for irradiation of biological materials.

At the beginning of each cyclotron run, the equipment was set up in the position used in the preceding run, and the beam intensity was measured as a function of cyclotron magnetic field (Fig. 8). The carbon particles, identified by observation of their pulse heights and ranges, were found to lie in a broad resonance. Toward higher magnetic fields they overlapped the sharp resonance of alpha particles accelerated from residual helium gas in the cyclotron tank, and toward lower magnetic fields they disappeared into a group of carbon particles of unknown trajectory that were not sensitive to the voltage on the cyclotron deflector. For bombardments with carbon ions the magnetic field was adjusted to give the maximum deflected beam of carbon particles with a minimum of alpha particles. The ionization produced by the spurious alpha particles was measured

by inserting sufficient absorber to stop all carbon particles. During bombardments frequent checks were made; the ionization due to alpha particles was kept to a maximum of 1% of the total, and was usually considerably lower.

After the cyclotron magnetic field was adjusted properly, a radioautograph of the beam was obtained to show what adjustments should be made in the position of the snout and ionization chambers in order to center the equipment on the beam and to give a visual estimate of the intensity distribution. Small x-ray films, wrapped in 0.0005-inch aluminum foil, were exposed to the beam by placing them in the blank position of the absorber wheel behind the first ionization chamber.

When the beam alignment was satisfactory, a Bragg ionization curve was obtained by plotting the ratio of charge collected in the analyzer ionization chamber to that collected in the monitor chamber as a function of the absorber thickness between the two ionization chambers. Simultaneously, individual particle pulses were counted in the two chambers, and a range curve was obtained by plotting the fraction of particles penetrating the absorber as a function of its thickness. Range and Bragg curves obtained in this manner are shown in Fig. 9. As explained above, the particles were actually counted in a thick chamber separated by a thin aluminum foil ( $1.6 \text{ mg/cm}^2$ ) from the chamber used in obtaining the ionization curve. Furthermore, with the discriminator settings used for these data, a minimum energy loss of 2.0 Mev was required in the second ionization chamber in order for a particle to be counted. It is estimated that this corresponds to a residual range for carbon particles of  $0.6 \pm 0.2 \text{ mg/cm}^2$  of aluminum. The collector foils of aluminum leaf and the gas of the ionization chambers accounted for an additional  $0.4 \text{ mg/cm}^2$  between the two analyzer ionization chambers. Hence in the range curve of Fig. 9 an additional absorber thickness of  $2.6 \text{ mg/cm}^2$  has been

added to each measured value in order to make the range curve correspond to the Bragg curve.

From the simultaneous collection of charge and the counting of particles in the ionization chambers it was possible to compute the average charge produced per particle. When this value was compared with that calculated for a carbon ion in nitrogen, the discrepancy of 2% was well within the expected uncertainty of  $\pm 6\%$ .

Because of the finite resolving time of the electronic equipment, for counting individual particle pulses it was necessary to limit the beam intensity to approximately 1/500 of that used in the biological experiments. Various attempts were made to lower the beam intensity by changing cyclotron operating conditions, with the hope that a low-intensity beam could be obtained with the same slit widths as the maximum-intensity beam used in the biological experiments. A comparison of the Bragg ionization curves showed that this was not possible, however, and the best physical data were obtained during runs in which biological irradiations were not attempted. For the data in Fig. 9 a 1/8-inch-diameter aperture was inserted in front of the first ionization chamber, and the first two slits were narrowed until a reasonable counting rate was observed. By comparing the range and Bragg curves measured simultaneously under different cyclotron running conditions and at different slit widths, the mean range of the carbon particles was found to correspond to a point on the Bragg curve of  $0.45 \pm .30$  times the maximum ionization. For the high-intensity beams used in the biological irradiations, for which individual particles could not be counted, this ordinate on the Bragg curve was used to determine the mean range and hence the energy and LET of the carbon particles.

While data for the range and Bragg curves were being obtained, particle pulses were also observed on the oscilloscope. The uniformity of pulse height

for small absorber thickness showed that the particles had a uniform average LET. As a result of range straggling, however, pulses of all heights were produced near the peak of the Bragg curve and beyond. Care was taken that the cell bombardments were made in the region of homogeneous LET.

After the measurement of range and Bragg curves was completed, the profile-scanning apparatus was inserted in front of the second ionization chamber, and the intensity distribution of the beam was obtained with the wide slits to be used for the cell bombardments. On the basis of these data further adjustments were made in the alignment of the apparatus. When the beam characteristics were considered satisfactory, the second analyzer ionization chamber was replaced by the dose-measuring quadrant chamber described above, and a fine adjustment was made in position in order to balance the ionization currents collected in the quadrants. Subsequent checks of beam centering were made frequently throughout the experiment. At this point the voltage saturation curve was checked, and a Bragg ionization curve was obtained with the dose-measuring chamber in its final geometry. For bombardment the biological samples, each consisting of a monolayer of cells plated on a block of agar, were placed in turn on a special receptacle just behind the ionization chamber. After the samples were irradiated, the Bragg-curve measurement was repeated and the temperature was determined.

#### CALCULATION OF DOSE AND LET WITH ESTIMATED UNCERTAINTIES

For determination of the dose delivered to the cells, the quantity actually measured was the voltage produced on a condenser by the charge collected from an ionization chamber. For each volt measured on the integrating electrometer, a dose  $D$  (in rads) was delivered to the cells, where  $D$  was calculated by the equation

$$D = \frac{C W S_m K P 10^5}{V \rho} \text{ rads/volt.}$$

In this expression  $C$  is the capacitance of the integrating condenser in farads,  $W$  is the energy in ev per ion pair for the formation of ions in dry nitrogen,  $S_m$  is the relative mass stopping power for the cell composition relative to that of nitrogen,  $K$  is the Bragg correction due to the stopping material located between the dose-measuring chamber and the irradiated cells,  $P$  is the correction for the nonuniformity of the beam,  $V$  is the volume of the ionization chamber in  $\text{cm}^3$ , and  $\rho$  is the density of the ionization-chamber gas in  $\text{g/cm}^3$ . The factor  $10^5$  comes from the conversion of units into rads, since 1 joule per gram is  $10^5$  rads. The quantities for each experiment with estimated standard deviations are given in Table I; their values are discussed below.

The most certain quantities in the dose measurement are the values  $C$  of the integrating capacitances (which were calibrated with an error of  $\pm 0.5\%$ ), the sensitive volume  $V$  of the ionization chamber ( $0.677 \pm 0.010$ ) and the density  $\rho$  of the gas (for which a temperature variation of  $\pm 1^\circ\text{C}$  was assumed). Together these uncertainties contribute less than 2% to the resultant standard error.

The correction factor  $P$  takes account of the nonuniform intensity distribution of the beam and the fact that the sample area is smaller than the area over which the dose is measured. The value of  $P$  was found by integrating the beam intensity graphically from profiles such as those in Figs. 4 and 5. The estimated uncertainty in  $P$  allows for variations in the position of the sample relative to the observed profile and for uncertainties in the dimensions of the sample. In addition, in Column 7 of Table I we have given the maximum variation in beam intensity over the sample. This figure was obtained by taking the high and low points of the beam profiles relative to their average. Even for the large

variation observed with alpha particles, this nonuniformity has small effect upon an exponential survival curve for survival levels above 5%.

The Bragg correction factor  $K$  is the ratio of ionization produced in nitrogen in the position occupied by the cells to that measured in the chamber. For each experiment it was determined graphically from a Bragg curve (similar to that in Fig. 9), measured with the quadrant ionization chamber just before or after the cell irradiation. The uncertainty in  $K$  was estimated from the consistency among different Bragg curves obtained during the same experiment, as well as the uncertainty in the thickness of absorber between the center of the ionization chamber and the center of the cells. The material between these two positions consisted of half of the gas of the ionization chamber ( $0.79 \text{ mg/cm}^2 \text{ N}_2$ ), the collector foil ( $3.56 \pm 0.04 \text{ mg/cm}^2 \text{ Al}$ ), the air between the collector foil and the cells ( $0.48 \pm 0.10 \text{ mg/cm}^2 \text{ air}$ ), and half the cell diameter ( $0.25 \pm 0.12 \text{ mg/cm}^2 \text{ tissue}$ ). The total is equivalent to  $5.44 \pm 0.33 \text{ mg/cm}^2$  of Al.

In order to convert the ionization produced in a gas to cellular dose it is necessary to multiply by the energy per ion pair  $W$  and the relative mass stopping power  $S_m$ . These quantities, as well as the linear energy transfer (LET), are functions of particle velocity. Hence it is necessary to determine the energy of the particles used in each experiment.

In the case of deuterons and alpha particles, for which individual particles could not be counted, the particle ranges were obtained from the measured Bragg curves. For the particular beams used here, we do not know what point on the Bragg curve corresponds to the mean range of the particles; hence the limits of error in the measured range were set by the peak of the Bragg curve on the one hand and the extrapolated ionization range on the other. Then the particle energies and the values of LET were obtained by using the range-energy curves of Aron, Hoffman, and Williams (5). The large uncertainty allowed in the range measurement produces

small errors in  $S_m$  and LET, since both quantities are slowly varying functions of particle energy.

In the case of carbon particles, the physical measurements in the previous section indicated that the mean range corresponded to a point on the Bragg curve of  $0.45 \pm 0.30$  times the maximum ionization. Since there are no published range-energy curves for carbon particles in aluminum, a semiempirical curve was constructed from the calculations by Smith for protons (6). The range extension due to charge pickup was estimated as  $7.5 \pm 2.5 \text{ mg/cm}^2$  from the data of Miller (7) and Barkas (8) for nuclear emulsion. The uncertainty in our range measurement was considerably larger than the error in the range-energy relation. For carbon particles, the uncertainty in the range measurement introduces a substantial error in the linear energy transfer. Fortunately the LET does not appear in the dose calculation; the corresponding error in  $S_m$  is less than 1% and is small compared with errors from other sources. The curves calculated by Snyder and Neufeld (9) were used to give the LET values in Table I for high-energy carbon ions. For these energies, where the stripped nuclear charge of six may be assumed (10), the values are in good agreement with those obtained from the semiempirical curves for protons (5, 11, 12).

For both alpha particles and carbon ions, the LET for each high-absorber point was obtained from the low-absorber value by taking the observed ratio of ionization for the two absorbers, with suitable corrections between tissue and nitrogen. The particle energies were then obtained from the energy-loss curves (5, 9) and were found to lie within the values obtained from the range estimates.

For each particle energy, Column 10 in Table I gives the energy per nucleon, i.e., the energy of a proton traveling with the same velocity. For

each proton energy, the value of the relative mass stopping power  $S_m$  was obtained from semiempirical curves (5, 12) as explained in Birge, Anger, and Tobias (11), but modified to fit the experimental data for the stopping power of water and nitrogen at low energies (13, 14, 15). The errors assigned to  $S_m$  in Table I allow for the rather large discrepancy between the calculated and experimental values of the stopping power of nitrogen for protons below 1 Mev, in addition to the estimated uncertainties of  $\pm 2\%$  each in the calculated values for water and nitrogen. The elemental composition used for yeast cells was 9.9% hydrogen, 11.5% carbon, 4.7% nitrogen, 72.3% oxygen, 0.03% sodium, 0.06% magnesium, 0.02% silicon, 0.6% phosphorus, 0.06% sulfur, 0.8% potassium, and 0.04% calcium (16, 17, 18). For the calculation of the energy loss of fast particles there is a negligible difference between this composition and that given by Lea for soft tissue (19). Both yeast and soft tissue have the same effective excitation potential as water, but they have 1% fewer electrons per gram. Hence the stopping power for these compositions is 1% less than that of water for particles of all energies (11).

For all particle energies above 2 Mev per nucleon the value of  $W$  for dry nitrogen was taken as  $34.8 \pm 0.9$  ev per ion pair (11, 20, 21, 22, 23). For the slow alpha particles (Experiment 1 b) the value  $W = 35.1$  was used (11).

For each experiment the last two columns in Table I give the calculated dose in rads per volt and the estimated percent standard deviation. The resultant error was obtained by summing the squares of the fractional errors for all the factors in the calculation (24). The resultant errors range from 4.5 to 8.8%. It should be noted that since the same experimental arrangement was used for all the cyclotron irradiations, some of the errors would be expected to cancel out in the calculations of relative biological effectiveness. Of course this does not apply to comparisons with other radiations.

### SUMMARY

The experimental apparatus used for the irradiation of yeast cells with cyclotron beams of 20-Mev deuterons, 40-Mev alpha particles, and 120-Mev carbon nuclei is described. The physical measurements necessary for an accurate determination of dose and average LET are also described. The dose calculation from ionization-chamber measurements is given, along with the estimated uncertainties that produce an over-all error ranging between 5 and 10%.

### ACKNOWLEDGMENTS

The authors wish to express their sincere appreciation to Professor Cornelius A. Tobias whose continued direction and support made this work possible. We would also like to express indebtedness to the late Professor Joseph G. Hamilton and Mr. G. Bernard Rossi for their encouragement and extended efforts in providing the carbon beam. In addition we thank Mr. W. Barclay Jones and members of the cyclotron crew, the various electronics groups, and members of the biophysics group, whose help throughout the work was invaluable.

REFERENCES

1. R. E. Zirkle, The radiobiological importance of linear energy transfer. In Radiation Biology, A. Hollaender, ed. Vol. I, pp. 315-350. McGraw-Hill, New York, 1954.
2. J. W. Boag, The relative biological efficiency of different ionizing radiations. Natl. Bur. Standards (U. S.) Rept. 2946 (1953).
3. J. F. Miller, J. G. Hamilton, T. M. Putnam, H. R. Haymond and G. B. Rossi, Acceleration of stripped  $C^{12}$  and  $C^{13}$  nuclei in the cyclotron. Phys. Rev. **80**, 486(L) (1950).
4. D. Walker and J. H. Fremlin, Acceleration of heavy ions to high energies. Nature **171**, 189-191 (1953).
5. W. A. Aron, B. G. Hoffman and F. C. Williams, Range-energy curves. AECU-663, Technical Information Service, Oak Ridge, Tenn., 1951.
6. J. H. Smith, Theoretical range-energy values for protons in air and aluminum. Phys. Rev. **71**, 32-33 (1947).
7. J. F. Miller, Reactions of fast carbon nuclei in photographic emulsions. (Thesis) Univ. of Calif. Rad. Lab. Rept. UCRL-1902 (1952).
8. W. H. Barkas, The range correction for electron pick-up. Phys. Rev. **89**, 1019-1022 (1953).
9. W. S. Snyder and J. Neufeld, On the passage of heavy particles through tissue. Radiation Research **6**, 67-78 (1957).
10. J. Knipp and E. Teller, On the energy loss of heavy ions. Phys. Rev. **59**, 661-669 (1941).
11. A. C. Birge, H. O. Anger and C. A. Tobias, Heavy charged-particle beams. In Radiation Dosimetry, G. J. Hine and G. L. Brownell, eds. pp. 623-665. Academic Press, New York, 1956.

12. M. Rich and R. Madey, Range-energy tables. Univ. of Calif. Rad. Lab. Rept. UCRL-2301, 1954.
13. H. K. Reynolds, D. N. F. Dunbar, W. A. Wenzel and W. Whaling, The stopping cross section of gases for protons, 30 - 600 kev. Phys. Rev. 92, 742-748 (1953).
14. A. B. Chilton, J. N. Cooper and J. C. Harris, The stopping powers of various elements for protons of energies from 400 to 1050 kev. Phys. Rev. 93, 413-418 (1954).
15. J. E. Brolley, Jr. and F. L. Ribe, Energy loss by 8.86-Mev deuterons and 4.43-Mev protons. Phys. Rev. 98, 1112-1117 (1955).
16. C. N. Frey, History and development of the modern yeast industry. Ind. and Eng. Chem. 22, 1154-1162 (1930).
17. G. Sykes (ed.), Constituents of bacterial culture media. Soc. of Gen. Microbiol., Special Report, Cambridge, 1956.
18. S. Spiegelman, H. O. Halvorson and R. Ben-Ishai, Free amino acids and the enzyme-forming mechanism. In A Symposium on Amino Acid Metabolism, W. D. McElroy and H. B. Glass, eds. pp. 124-170. Johns Hopkins Press, Baltimore, 1955.
19. D. E. Lea, Actions of Radiations on Living Cells, The Macmillan Co., New York, 1947.
20. W. P. Jesse and J. Sadauskis, Ionization in pure gases and the average energy to make an ion pair for  $\alpha$  and  $\beta$  particles. Phys. Rev. 97, 1668-1670 (1955).
21. W. P. Jesse and J. Sadauskis, Absolute energy to produce an ion pair by beta particles from  $S^{35}$ . Phys. Rev. 107, 766-771 (1957).

22. W. C. Barber, Specific ionization by high-energy electrons. Phys. Rev. 97, 1071-1077 (1955).
23. J. Weiss and W. Bernstein, The current status of W, the energy to produce one ion pair in a gas. Radiation Research 6, 603-610 (1957).
24. R. T. Birge, The propagation of errors. Am. J. Phys. 7, 351-357 (1939).

FOOTNOTES

1. This work was supported by the U. S. Atomic Energy Commission and the Cancer Fund of the State of California. A preliminary report of part of this work is contained in J. A. Sayeg, "The effect of highly ionizing radiations on cell survival". (Thesis), Univ. of Calif. Rad. Lab. Report, UCRL-2293 (1954).
2. Present address: Los Alamos Scientific Laboratory, Los Alamos, New Mexico.

FIGURE CAPTIONS

- Figure 1. Schematic plan view of the cyclotron and the equipment used for biological experiments.
- Figure 2. Photograph showing the irradiation equipment connected to the exit port of the cyclotron.
- Figure 3. Typical voltage saturation curves for the dose-measuring quadrant ionization chamber.
- Figure 4. Profiles of the carbon-particle beam used in Experiment 2.
- Figure 5. Profiles of the alpha-particle beam used in Experiment 1.
- Figure 6. A schematic diagram of the quadrant ionization chamber plates connected to the electrometers.
- Figure 7. Schematic diagram of the dose-measuring quadrant ionization chamber showing the position of the biological sample relative to the cyclotron beam.
- Figure 8. A graph of the ionization-chamber current as a function of the current in the cyclotron magnet coils.
- Figure 9. A Bragg ionization curve and range curve for carbon particles.

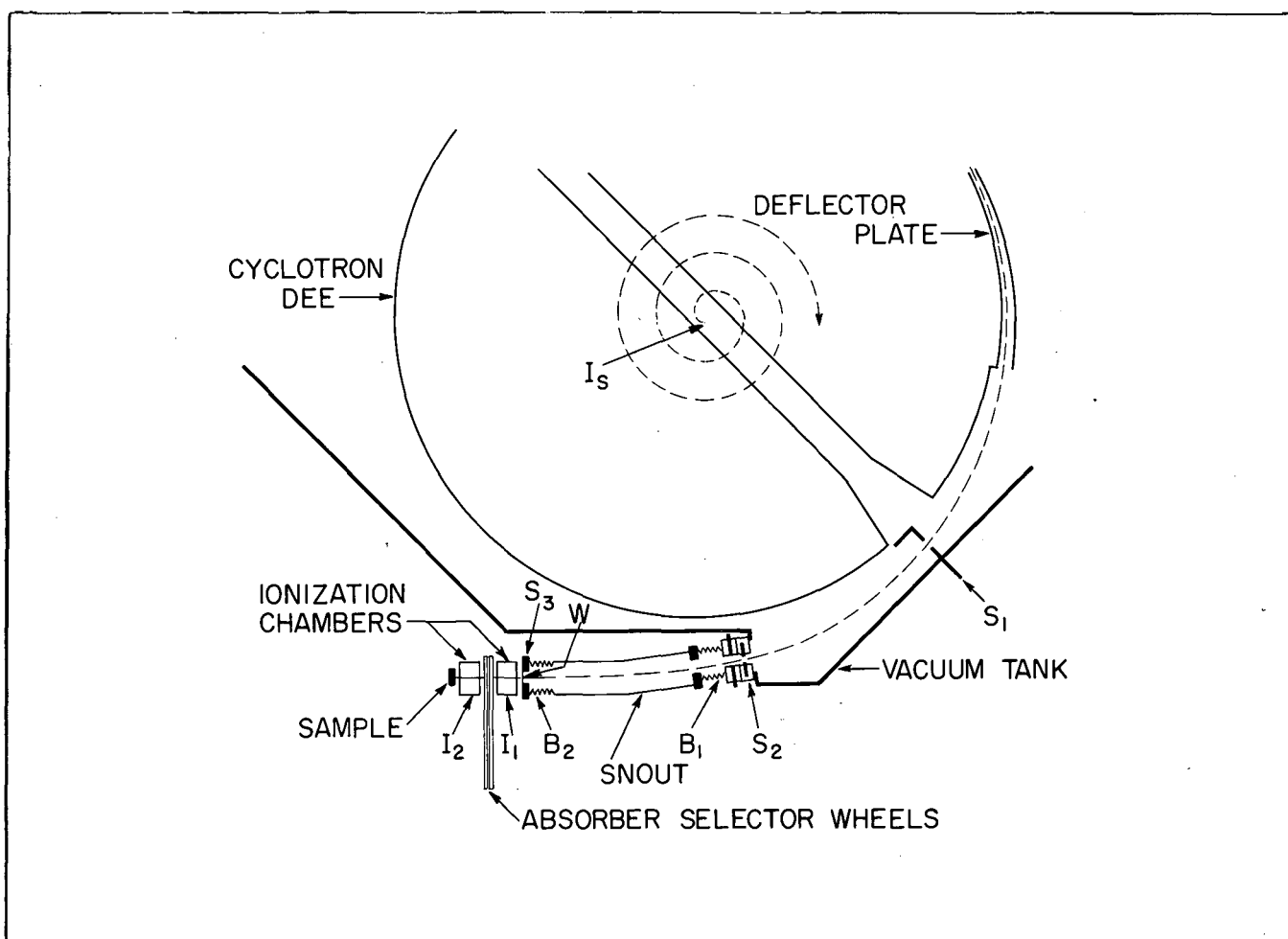


Fig. 1

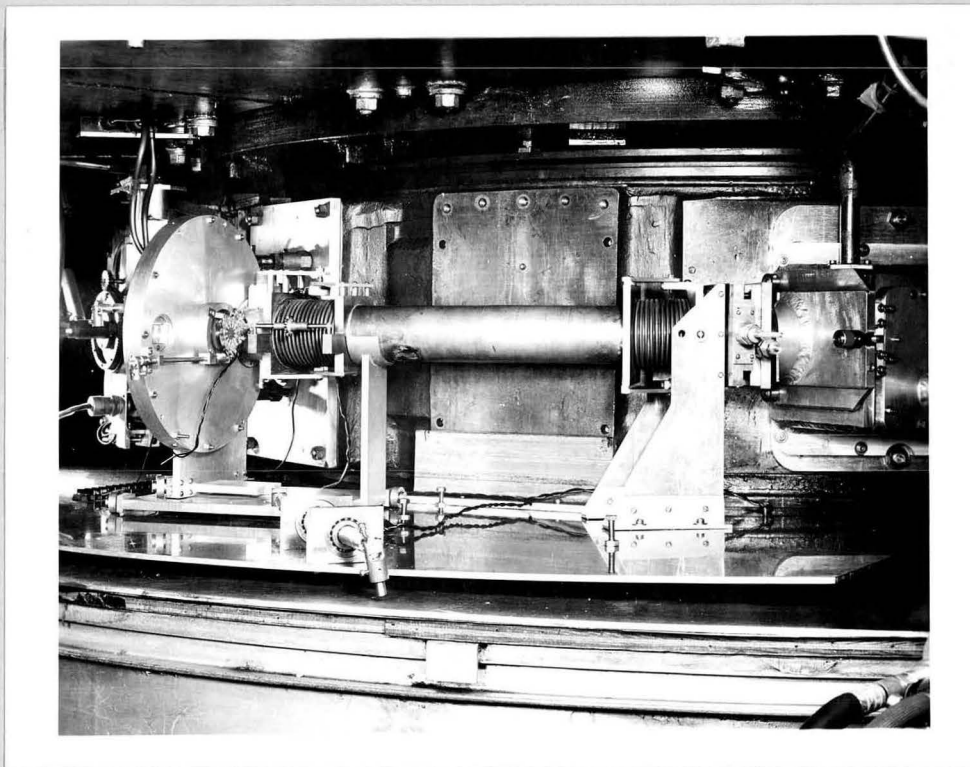


Fig. 2

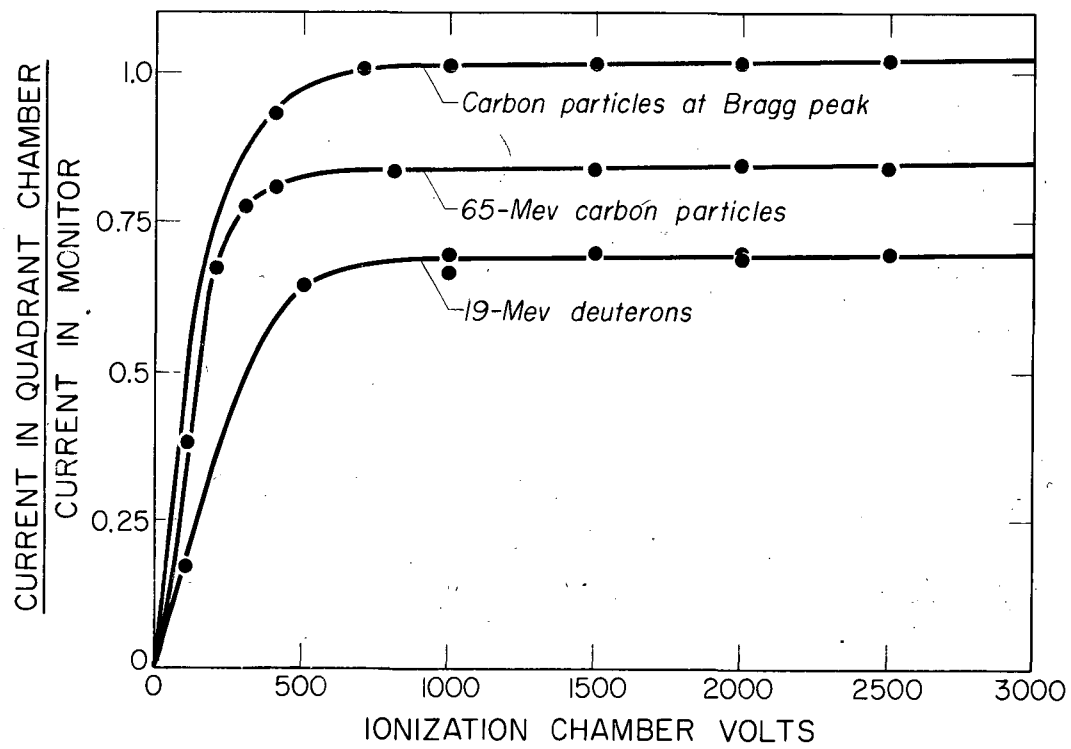


Fig. 3

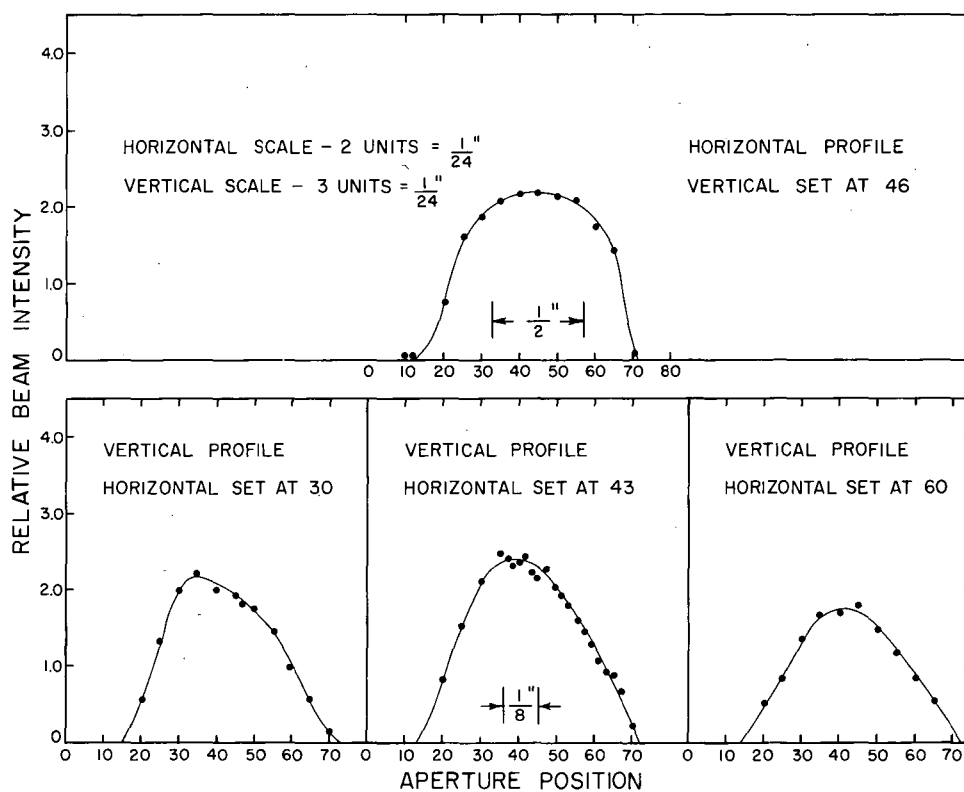


Fig. 4

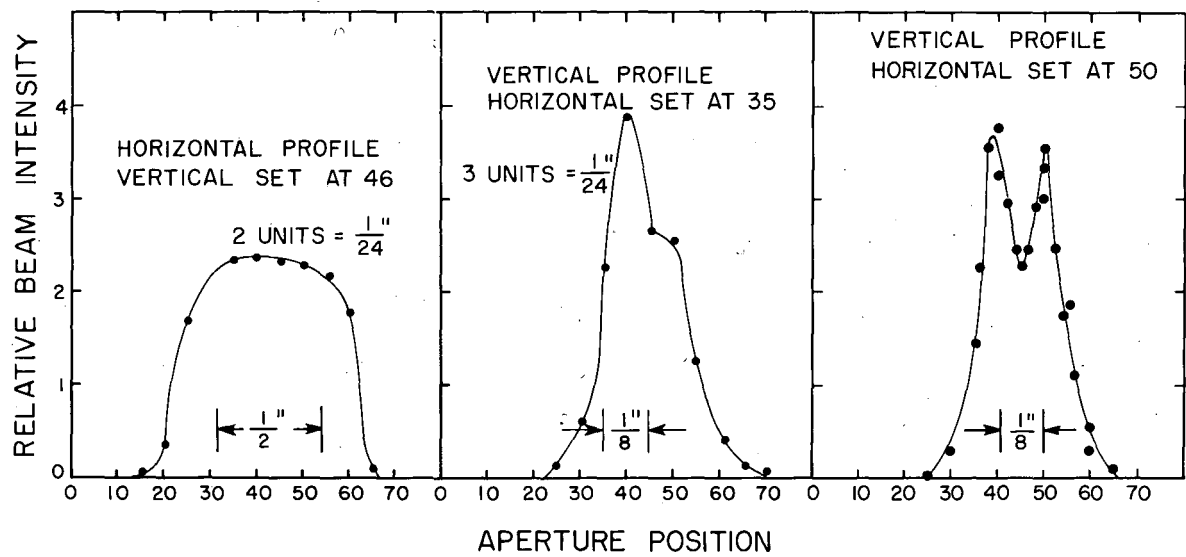


Fig. 5

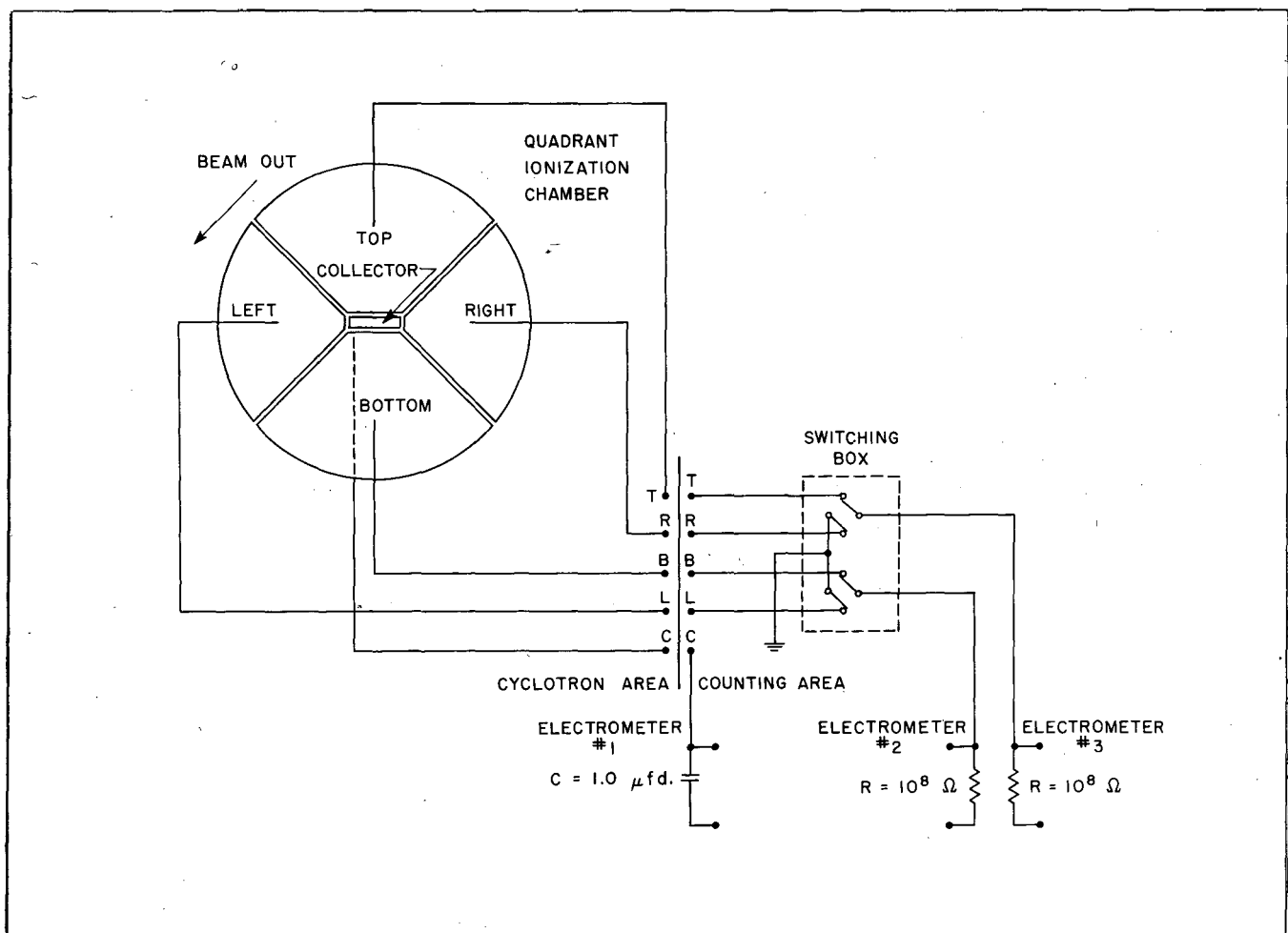


Fig. 6

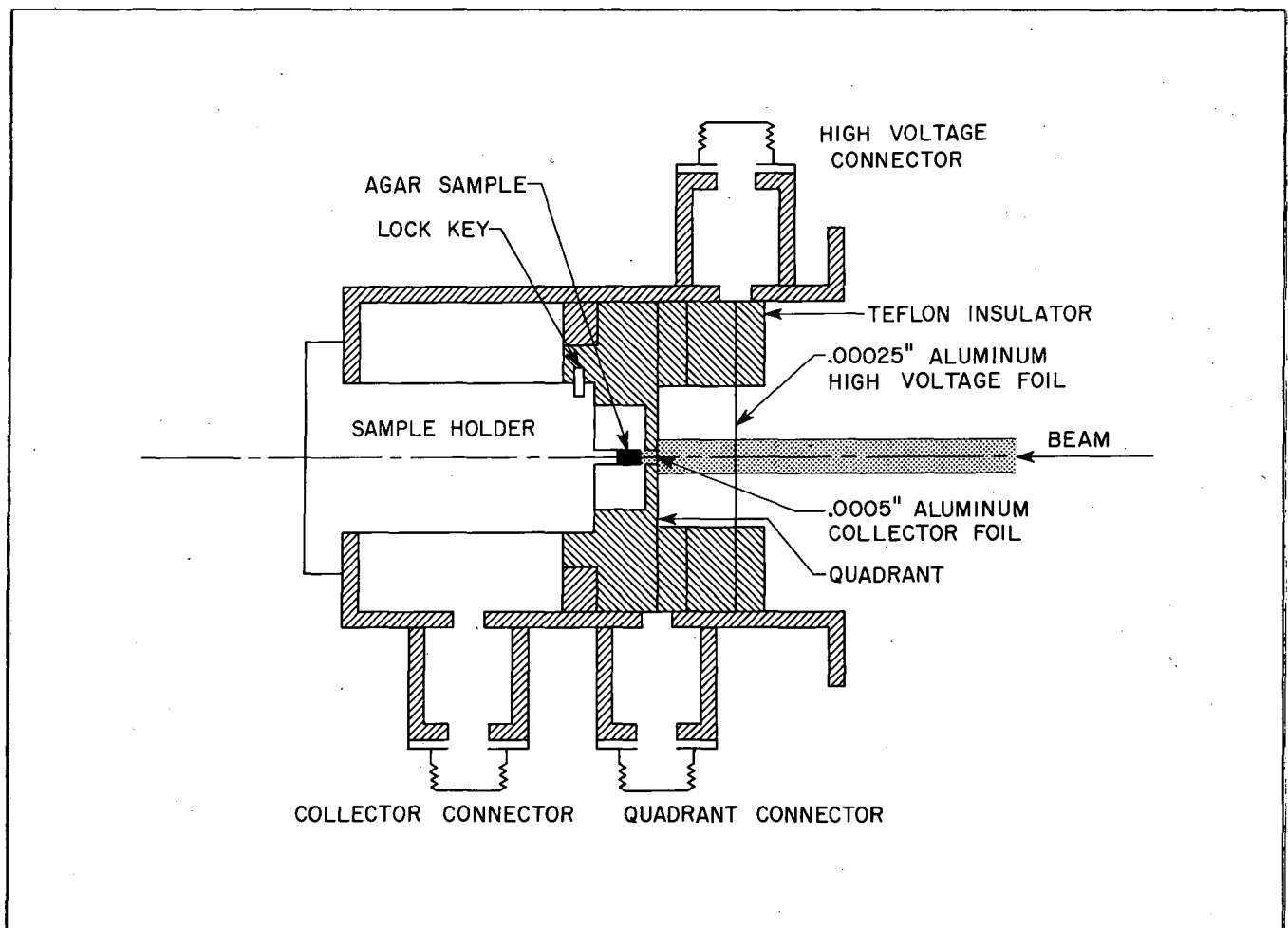


Fig. 7

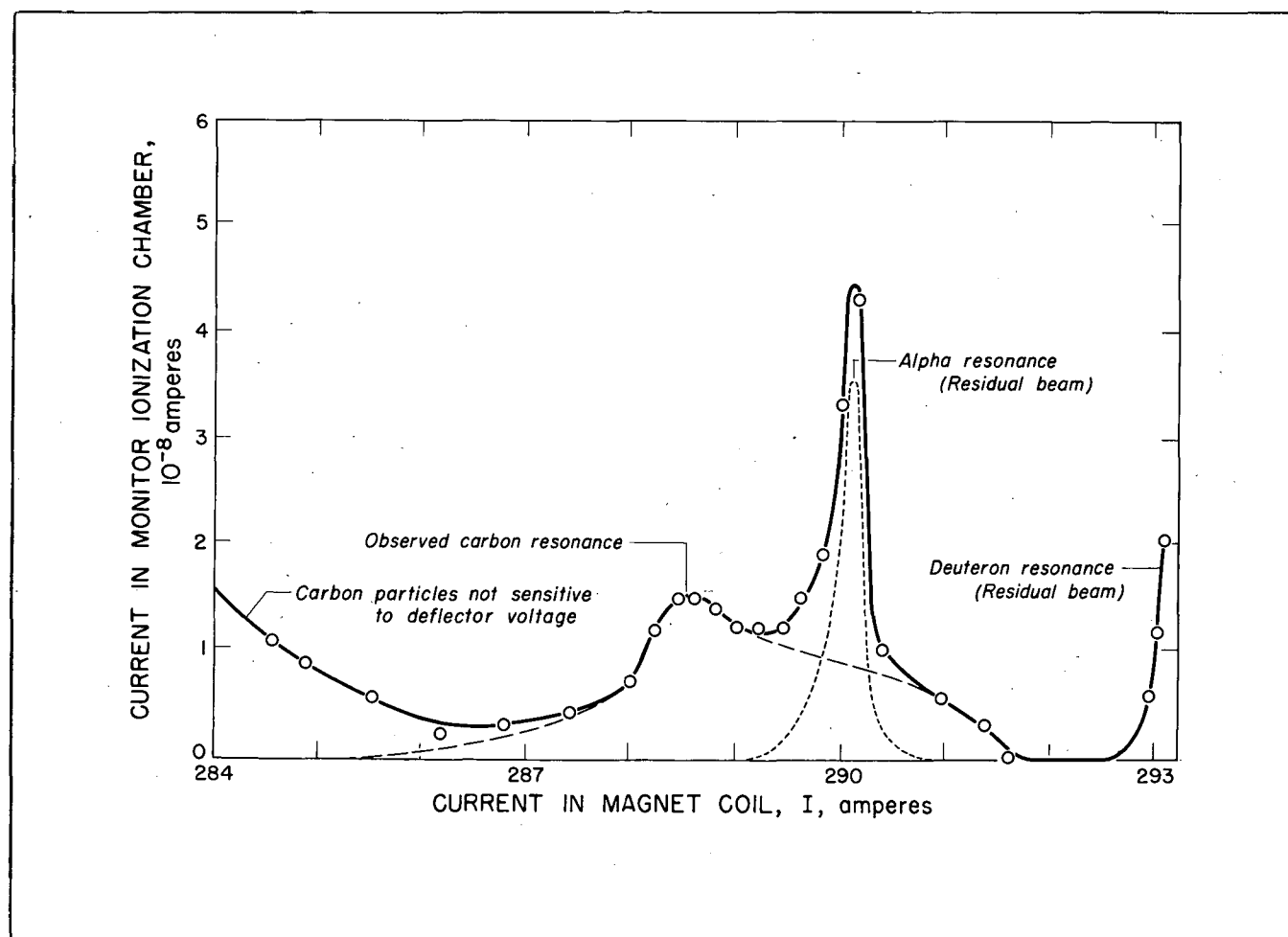


Fig. 8

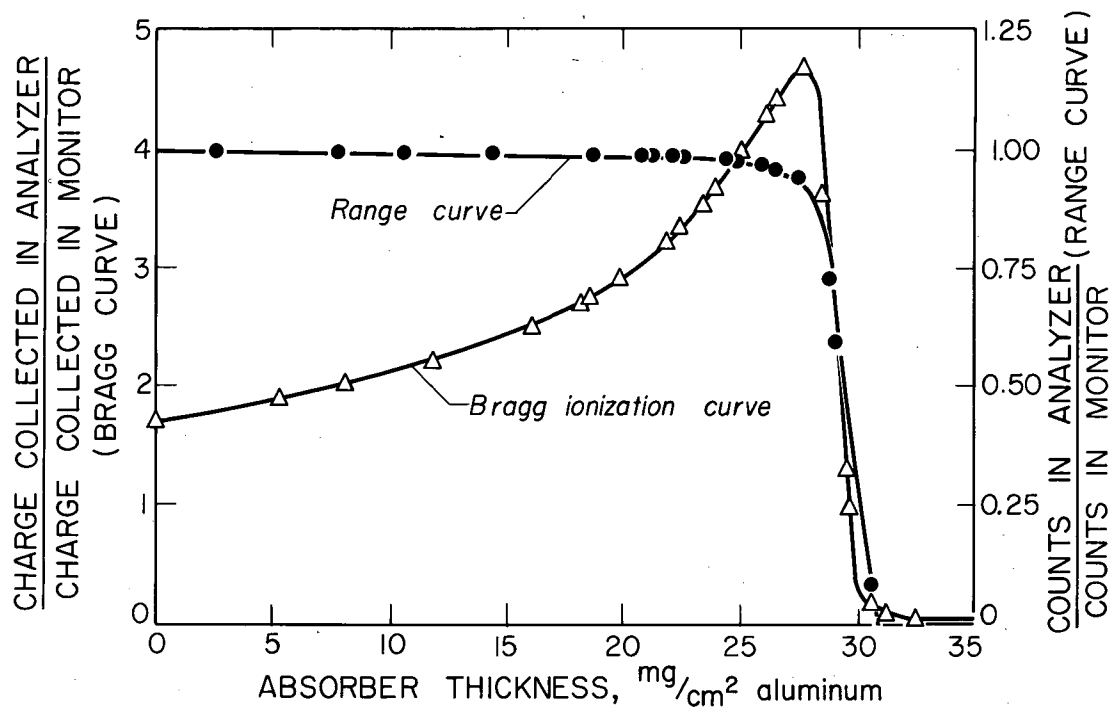


Fig. 9

Table I

## DOSE CALCULATION FACTORS FOR THE CYCLOTRON BEAMS

| 1                         | 2                           | 3                                                | 4                                                               | 5                                                         | 6                                    | 7                                    | 8                                  | 9                                      | 10                                | 11                                                                            | 12                                                  | 13                           | 14                            |
|---------------------------|-----------------------------|--------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------|--------------------------------------|--------------------------------------|------------------------------------|----------------------------------------|-----------------------------------|-------------------------------------------------------------------------------|-----------------------------------------------------|------------------------------|-------------------------------|
| Experi-<br>ment<br>number | Bom-<br>barding<br>particle | Absorber<br>thickness<br>(mg/cm <sup>2</sup> Al) | Integrat-<br>ing capac-<br>itance C<br>(10 <sup>-6</sup> farad) | Density<br>of N <sub>2</sub> gas<br>(mg/cm <sup>3</sup> ) | Profile<br>correction<br>factor<br>P | Beam<br>uniformity<br>over<br>sample | Bragg<br>correction<br>factor<br>K | Particle<br>energy<br>at cell<br>(Mev) | Energy<br>per<br>nucleon<br>(Mev) | Relative mass<br>stopping power<br>S <sub>m</sub> tissue to<br>N <sub>2</sub> | Average LET<br>in cells<br>(Mev cm <sup>2</sup> /g) | Dose<br>D<br>(rads/<br>volt) | Error<br>in dose<br>(percent) |
| 1a                        | Alpha                       | 56.3                                             | 1.095                                                           | 1.138                                                     | 1.00 ±0.05                           | ±22%                                 | 1.022±0.011                        | 26.8±0.7                               | 6.7±0.2                           | 1.153±0.036                                                                   | 258± 6                                              | 5850                         | 6.7                           |
| 1b                        | Alpha                       | 130.3                                            | 1.095                                                           | 1.138                                                     | 1.00 ±0.05                           | ±22%                                 | 1.340±0.050                        | 5.9±0.8                                | 1.5±0.2                           | 1.210±0.067                                                                   | 850±100                                             | 8130                         | 8.8                           |
| 1c                        | Deuteron                    | zero                                             | 1.095                                                           | 1.138                                                     | 1.020±0.015                          | ±14%                                 | 1.00 ±0.00                         | 19.1±0.5                               | 9.6±0.2                           | 1.144±0.033                                                                   | 48± 2                                               | 5790                         | 4.5                           |
| 2a                        | Carbon                      | zero                                             | 1.095                                                           | 1.127                                                     | 1.024±0.005                          | ± 4%                                 | 1.099±0.008                        | 65 ± 5                                 | 5.4±0.4                           | 1.161±0.039                                                                   | 2680±300                                            | 6550                         | 4.6                           |
| 2b                        | Carbon                      | 13.4                                             | 1.095                                                           | 1.127                                                     | 1.024±0.005                          | ± 4%                                 | 1.298±0.033                        | 30 ±10                                 | 2.5±0.8                           | 1.186±0.051                                                                   | 4450±540                                            | 7900                         | 5.9                           |
| 3a                        | Carbon                      | zero                                             | 1.057                                                           | 1.150                                                     | 1.027±0.010                          | ± 6%                                 | 1.067±0.016                        | 67 ± 5                                 | 5.6±0.4                           | 1.159±0.038                                                                   | 2600±200                                            | 5990                         | 4.8                           |
| 3b                        | Carbon                      | 16.1                                             | 1.057                                                           | 1.150                                                     | 1.027±0.010                          | ± 6%                                 | 1.353±0.027                        | 24 ± 9                                 | 2.0±0.7                           | 1.194±0.056                                                                   | 5080±460                                            | 7840                         | 6.1                           |